Patrick C. Kung, Ph.D.
President & CEO

PhytoCeutica Inc.

6383 '00 OCT 10 P12:12

October 6, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

via FedEx

Dear Sirs/Madame,

My colleagues and I have reviewed the draft of "Guidance for Industry: Botanical Drug Products" released for public comments on August 10,2000 by Center of Drug Evaluation and Research of the FDA. We applaud the tireless efforts for which staff at the FDA have labored for drafting the document. It is clear that the document represents a major progress toward finalizing the Guidance. It would benefit citizens around the world, especially those living in developing countries, as well as the entire pharmaceutical industry .

Upon reviewing the draft, we have come up with a comprehensive list of comments to relevant sections of the documents as shown on the Attachment. We would appreciate your careful review and consideration of the comments.

We look forward to the publication of the final document in the near future.

Sincerely,

PhytoCeutica, Inc., 5 Science Park, Box 13, New Haven, CT. 06511 USA
TEL: 203-777-3462 FAX: 203-777-3538

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Attachment

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Submitted by: PhytoCeutica, Inc.
5 Science park, Suite 13
New Haven, CT 06511
Tel: 203- 777-3462
Fax: 203- 777 -3538
Contact: Tahmun Su, Ph.D.
Vice President of Operation

Re: Comments on Docket Number HFA-305; "Guidance for Industry: Botanical Drug Products"

Comments:

General Comment: Through the text, active ingredients, representative markers are used. These terms are derived from the single chemical medicine. We respectively recommend that the document begins with a section discussing the characteristics of botanical drugs; the most significant features of botanical drugs are 1) it is a multi-chemical or multi-component medicine, 2) pharmacological and toxicological properties of a botanical drug may be attributable to more than a single chemical, and 3) there are ample examples in the history of medicine, in which the mechanism or scientific theories backing the medicine were developed years after the efficacy and safety of a novel medicine had been validated in a robust and rigorous clinical trial. While the state-of-the art of botanical drugs is evolving, institutions should apply the modem applicable technology and science to the advancement of botanical drugs for the welfare of suffered human subjects.

Page 2, first paragraph: definition of botanicals

We respectively recommend that the definition is expanded to include fungi products produced in a bioreactor fungi, such as Cordyceps sinensis,. Such inclusion would protect the fungus from becoming extinct from over-harvesting in the wildness.

Also, will a genetically modified (GM) plant be excluded? ?we respectively recommend that it is excluded

Page 4, Line 7 and 8 :

We respectively recommend that the marketing exclusivity is extended for 7 years or 5 years from the time of approval. The investment to get an NDA approved has steadily increased at a much higher rate than that of inflation and the extension requested would serve as an adequate incentive.

Page 5, Line 10: revision of regulation

We respectively inquire the estimated timing of publication of the proposed revisions.

Page 6, Line 4: definition of "generally recognized ---"

W e respectively inquire about the source of document in which the term of "generally recognized" is defined. Specifically, whether documented prior human use of an herbal formula and/or its constituent herb can be cited as generally recognized?

Line 9: adequate CMC

We respectively recommend that the word "adequate" be changed to "attainable CMC with the state-of-art and validated technology"

Line 17: "intended for research purposes"

We respectively inquire whether a product intended for nutritional or dietary supplement uses would require an IND for research purposes in human.

Page 7, Line 5: evidence of safety

We respectively inquire whether the safety evidence from a foreign country is acceptable?

Line 10 and Line 13: "anywhere"

We respectively inquire whether "anywhere" is limited to the U.S. If not, then may the word could change to "anywhere in the world".

Page 10, Line 1: definition of "limit"

We respectively inquire about the inclusion of the definition of "limit". For example, does it include the limit of chemical components, limit of potency, or limit of marker substances? Additional clarification would be helpful.

Line 4,

When possible, efforts should also be made to identify active constituents during Phase 3 studies.

The word " possible" is not appropriate here because it is always "possible" to make effort to do the identify .....Identification of active constituents presented in botanical substance or drug is not a matter of "possible" but rather whether it is attainable or feasible" at all. Furthermore, the identification of active constituents may not reflect the actual pharmacological activity of the botanical drug.

We respectively suggest to change of word " possible" to word " attainable or feasible ".

Last paragraph:

We respectively recommend that the agency amend the definition of botanical drugs (page 2) to include the addition or synthetic and purified substance or, animal parts, so the language is consistent.

Page 11, Line 5-8,

Does FDA mean that it is necessary for a botanical substance manufacturer to file DMF to FDA when the sponsor of IND application is different from the manufacturer? Does FDA mean that the facility of the manufacturer be subjected to FDA inspection prior to IND submission?

Page 12, the last line: "official proof"

We respectively inquire whether an official statement signed by CEO/President of a company is accepted as "official proof" of the annual sales. If not, what type of proof in the U.S> or in a foreign country is acceptable.

Page 13, Line 10: " a trained botanist"

We respectively inquire the qualification of being " a trained botanist" defined in the U.S. and in a foreign country.

Page 16, Line 8: "representative markers"

We respectively inquire whether "representative markers" is synonymous with chemical markers mentioned throughout the documents.

Page 18, Line 15,

At least 100 g of specimen of raw materials used to produce botanical substance or product should be retained and kept at suitable temperature to insure its stability for a period of time 2 years after the approval of the NDA or discontinuation of IND. (This is the same length of time for keeping the subject's source data obtained in clinical trial)

Page 25, Line 18: A voucher specimen of the plant or plant parts should be---------.

Since both botanical drug substance and product also include those materials other than plants such as fungi, the "plant or plant parts" should be changed to " the raw materials that are used to produce botanical drug substance should be retained and kept at suitable temperature to insure its stability for a period time 2 years after the approval of the NDA or discontinuation of IND.

Page 25, Line 29: The quality control tests applied by the botanical raw material supplier, including the following specifications--------;

Since the raw material supplier (or grower) in general does not have adequate laboratory facilities to perform analysis with sophisticated equipment to meet the specifications listed on line 2,3,5, 7,8,9,10 and 11 on page 26. we suggest that the raw material supplier provides the following information: the name of grower, location of cultivation, time of harvest, botanical identification and any physical and chemical pre-treatment process and storage condition. Botanical drug substance manufacturer shall be responsible for establishing acceptance raw material specifications to insure of consistency in specification from batch to batch substance production.

Page 26, Line 26,

We respectively recommend to insert " should be" after IX.B.1.a----------.

Page 27, Line 1,

We respectively recommend that the manufacturer should perform not only the identification test of the receiving raw materials but also perform all the analysis for the acceptability of the raw materials based on established in-house raw material specifications.

Page 27, Line 24,

We respectively recommend to add "if it is available or attainable" after the word "Biological assay"

Line 33: residual pesticide----

We respectively inquire which standard to follow, i.e., that of WHO, or that of USP.

Page 29, Line 4,

We respectively recommend to add "if it is available or attainable" after the word "Biological assay"

Page 30, line 5: All chemical constituents present in drug substance----

Finding all chemical constituents present in the botanical drug substance or product is only limited by the detection ability of the detector to detect them all. Therefore, the number of the components appearing in chemical fingerprinting depends on the detectors used in the analysis. For example, the HPLC chemical fingerprinting of the same botanical substance obtained at one wavelength could be different from that obtained from the other wavelength. Similarly, the chemical fingerprinting obtained from a LCEC detector will be drastically different from that of UV detector.

We respectively recommend that the text is changed to " Spectroscopic and/or chromatographic fingerprinting from batch to batch should be qualitatively and quantitatively comparable when the same analytical protocol and equipment is employed."

Page 30, Line 9:

We respectively recommend to change to " ...including identification and assay for active constituents if attainable, identification and assay for characteristic markers, and/or biological assay if available, should be established------

Page 30, Line 22:

"to demonstrate the mass balance of the test sample" : In order to make a mass balance of a given unknown mixture of chemicals in the sample, it is necessary to know the molar response of each component in the mixture. Therefore, we respectively recommend that this sentence is deleted.

Page 30, Line 27: Stability

Due to the complexity of the components in botanical drug substance, such as carbohydrate, amino acid, and other organic compounds, it is not practical as well as not possible to develop analytical protocols to detect the degradents formed during the storage. We respectively recommend to use chemical marker(s) and/or bioassay(s), if available or attainable, to monitor the stability of the drug substance/product under stress conditions; the degradent formation should be expressed as the % of total area appeared before and after the stress condition using a chromatographic analysis and the % of increase should meet the release specification.

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